

Amendments to the Specification

Please replace paragraph [0001] on page 1 with the following amended paragraph:

[0001] This application claims benefit of United States provisional application No. 60/~~377,510~~410,010, filed September 9, 2002, the disclosure of which is incorporated herein by reference.

Please replace paragraph [0021] on page 8 with the following amended paragraph:

[0021] The following abbreviations are used in ~~Figures 1 and 2~~ Figures 1A, 2A, 3A and 3B:

"Atom type" refers to the element whose coordinates are measured. The first letter in the column defines the element.

"Res" refers to the amino acid residue in the molecular model.

"X, Y, Z" define the atomic position of the element measured.

"B" is a thermal factor that measures movement of the atom around its atomic center.

"Occ" is an occupancy factor that refers to the fraction of the molecules in which each atom occupies the position specified by the coordinates. A value of "1" indicates that each atom has the same conformation, i.e., the same position, in the molecules.

Please replace paragraph [0022] on page 9 with the following amended paragraph:

[0022] Figure 1A (1A-1 to 1A-100) lists the atomic coordinates for native human ACE2 (amino acid residues 19-740 of full-length human ACE2 protein ~~(SEQ ID NO: 4)~~ with residues 621-626 and 661-705 of full-length human ACE2 protein ~~(SEQ ID NO: 4)~~ built as alanines; residues 804-823 represent a section of residues which are built as alanines into the electron density and cannot be assigned exact amino acid numbers (residues 627 to 660 or residues 706 to 740 may include residues 804-823)) as derived from X-ray diffraction of the crystal before individual B-factor refinement. The coordinates are shown in Protein Data Bank (PDB) format. Residues NAG, TIP and ZN2 represent N-acetyl glucosamine (NAG) groups, water and zinc ion, respectively.

Please replace paragraph [0023] on page 9 with the following amended paragraph:

[0023] Figure 2A (2A-1 to 2A-100) lists the atomic coordinates for native human ACE2 (amino acid residues 19-740 of full-length human ACE2 protein ~~(SEQ ID NO: 4)~~ with residues 621-626 and 661-705 of full-length human ACE2 protein ~~(SEQ ID NO: 4)~~ built as alanines; residues 804-823 represent a section of residues which are built as alanines into the electron density and cannot be assigned exact amino acid numbers (residues 627 to 660 or residues 706 to 740 may include residues 804-823)) as derived from X-ray diffraction of the crystal after individual B-factor refinement. The coordinates are shown in Protein Data Bank (PDB) format. Residues NAG, TIP

and ZN2 represent N-acetyl glucosamine (NAG) groups, water and zinc ion, respectively.

Please replace paragraph [0024] on pages 9-10 with the following amended paragraph:

[0024] Figure 3A (3A-1 to 3A-89) lists the atomic coordinates for human ACE2 (amino acid residues 19-613 of full-length human ACE2 protein ~~(SEQ ID NO: 4)~~) complexed with (S, S) 2-{1-carboxy-2-[3-(3,5-dichloro-benzyl)-3H-imidazol-4-yl]-ethylamino}-4-methyl-pentanoic acid (inhibitor1) as derived from X-ray diffraction of the crystal and refined to 3.3 Å resolution. The coordinates are shown in Protein Data Bank (PDB) format. Residues XX5, ZN. CL, and HOH represent inhibitor1, zinc ion, chloride ion and water, respectively.

Please replace paragraph [0025] on page 10 with the following amended paragraph:

[0025] Figure 3B (3B-1 to 3B-95) lists the atomic coordinates for human ACE2 (amino acid residues 19-740 of full-length human ACE2 protein ~~(SEQ ID NO: 4)~~ with residues 621-626 and 661-705 of full-length human ACE2 protein ~~(SEQ ID NO: 4)~~ built as alanines; residues 804-823 represent a section of residues which are built as alanines into the electron density and cannot be assigned exact amino acid numbers (residues 627 to 660 or residues 706 to 740 may include residues 804-823)) complexed with (S, S) 2-{1-carboxy-2-[3-(3,5-dichloro-benzyl)-3H-imidazol-4-yl]-ethylamino}-4-methyl-pentanoic acid (inhibitor1) as derived from X-ray diffraction of the crystal and refined to 3.0 Å resolution. The coordinates are shown in Protein Data Bank (PDB) format. Residues NAG, TIP, XX5, ZN.

And CL represent N-acetyl glucosamine (NAG) groups, water, inhibitor1, zinc ion, and chloride ion, respectively.

Please replace paragraph [0026] on pages 10-11 with the following amended paragraph:

[0026] Figure 4 shows the primary sequence alignments for amino acid residues 19 to 613 of human ACE2 (SEQ ID NO: 4)(full-length sequence: SwissProt Q9NRA7, ~~SEQ ID NO: 4~~), the corresponding residues of the C-terminal catalytic domain of human somatic ACE (SEQ ID NO: 5) and the corresponding residues of germinal or testicular human ACE (tACE) (SEQ ID NO: 6; the numbering used for the tACE sequence follows Natesh et al., *Nature* 421, pp. 551-4 (2003)). The mature metallopeptidase domain of human ACE2 corresponds to residues 19 to 613. The Clustal W Alignment Tool (Higgins et al., *Methods Enzymol.* 266, pp. 383-402 (1996)) was used for these sequence alignments. The secondary structural elements of human ACE2 are denoted by ----> for helical sections and beta strands are denoted by ---●. Helices 1-3, 10-13 and 15, and beta strands 4-6 are found in subdomain I while helices 4-9, 14 and 16-23, and beta strands 1-3 and 7 are found in subdomain II. Residues which are identical between human ACE2, and human sACE and tACE are marked with an asterisk at the bottom of the sequences. The six predicted N-linked glycosylation sites for the metallopeptidase region of ACE2 are denoted by the strikethrough symbol, ~~N~~. The beginning of the collectrin homology domain (Zhang et al., *J. Biol. Chem.* 276, pp.17132-17139 (2001)) is denoted by the inverted triangle symbol, ▼. Zinc binding residues include: H374, H378, and E402(ACE2 sequence numbers given). Chloride ion binding residues

include: R169, W477 and K481(ACE2 sequence numbers given) and additional chloride binding residues that occur for only sACE and tACE include Y224 and R522 (tACE sequence numbers given).

Please replace paragraph [0047] on page 18 with the following amended paragraph:

[0047] The term "ACE2-like" refers to all or a portion of a molecule or molecular complex that has a commonality of shape to all or a portion of the ACE2 protein. For example, in the ACE2-like active site binding pocket, the commonality of shape is defined by a root mean square deviation of the structure coordinates of the backbone atoms between the amino acids in the ACE2-like active site binding pocket and the ACE2 amino acids in the ACE2 active site binding pocket (as set forth in ~~Figures 3A or 3B~~ Figure 3A or 3B). Depending on the set of ACE2 amino acids that define the ACE2 active site binding pocket, one skilled in the art would be able to locate the corresponding amino acids that define an ACE2-like active site binding pocket in a protein based on sequence or structural homology.

Please replace paragraph [0061] on pages 22-23 with the following amended paragraph:

[0061] The term "homologue of ACE2" or "ACE2 homologue" refers to a molecule that has a domain having at least 40%, 60%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or greater than 99% sequence identity to the catalytic domain of human ACE2 protein. Preferably, the molecule has a domain having 60%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or greater than 99% sequence identity to the catalytic domain of human ACE2 protein. The homologue can be ACE2, ACE, germinal

ACE, somatic ACE from human, with conservative substitutions, conservative additions or deletions thereof. The homologue can be ACE2, ACE, germinal ACE, somatic ACE from another animal species. Such animal species include, but are not limited to, mouse, rat, a primate such as monkey or other primates. The human ACE2 protein can be human ACE2 full-length protein (amino acids 1-805 of human ACE2 protein SEQ ID NO: 4); the extracellular domain with amino acids 1-740 of human ACE2 protein SEQ ID NO: 4; amino acids 1-611 of human ACE2 protein SEQ ID NO: 4; amino acid residues 19-611 of SEQ ID NO: 4. The human somatic ACE can be the full-length protein with 1306 residues, the C-terminal catalytic domain or N-terminal catalytic domain. The human germinal ACE can be the full-length protein with 732 residues or the catalytic domain. See A. J. Turner and N. M. Hooper, *Trends in Pharmacological Sciences*, 23, 177-183 (2002), incorporated herein by reference.

Please replace paragraph [0078] on pages 29-30 with the following amended paragraph:

[0078] As used herein, the ACE2 protein in the crystallizable or crystal compositions can be full-length human ACE2 protein (amino acids 1-805 of human ACE2 protein SEQ ID NO: 4); an extracellular domain of human ACE2 protein (amino acids 1-740 of human ACE2 protein SEQ ID NO: 4; amino acids 1-611 of human ACE2 protein SEQ ID NO: 4; amino acid residues 19-611 of human ACE2 protein SEQ ID NO: 4); or the aforementioned with conservative substitutions, deletions or additions, to the extent that the protein substitutions, deletions or additions maintains an ACE2 activity, preferably the protein with substitutions, deletions or additions is at least 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical to one of the aforementioned. Preferably, the protein with substitutions, deletions or additions is at least

60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical to one of the aforementioned.

Please replace paragraph [0098] on page 36 with the following amended paragraph:

[0098] After the ACE2-inhibitor1 complex structure was refined, it was also possible to predict the binding pocket from the structure coordinates of this complex (~~Figures 3A or 3B~~ Figure 3A or 3B).

Please replace paragraph [0099] on page 37 with the following amended paragraph:

[0099] In another embodiment, the binding pocket comprises amino acids N149, D269, R273, H345, P346, A348, D367, H374, E375, H378, E402, F504, H505, Y510 and Y515 according to the structure of ACE2-inhibitor1 complex in ~~Figures 3A or 3B~~ Figure 3A or 3B. The above-identified amino acid residues were within 5 Å ("5 Å sphere amino acids") of the inhibitor bound in the binding pockets. These residues were identified using the program QUANTA (Molecular Simulations, Inc., San Diego, CA ©1998,2000; Accelrys ©2001, 2002), O (T.A. Jones et al., *Acta Cryst.*, A47, pp. 110-119 (1991)) and RIBBONS (Carson, *J. Appl. Cryst.*, 24, pp. 958-961 (1991)), which allow the display and output of all residues within 5 Å from the inhibitor.

Please replace paragraph [0100] on page 37 with the following amended paragraph:

[0100] In another embodiment, the binding pocket comprises amino acids L144, E145, N149, M152, A153, D269, M270, W271, R273, F274, N277, H345, P346, T347, A348, K363, T365, D367, D368, T371, H374, E375, H378, E402, F504, H505, Y510, F512,

R514, Y515 and R518 according to the structure of ACE2-inhibitor1 complex in ~~Figures 3A or 3B~~ Figure 3A or 3B. These amino acids residues were within 8 Å ("8 Å sphere amino acids") of the inhibitor bound in the ATP-binding pockets. These residues were identified using the programs QUANTA, O and RIBBONS, *supra*.

Please replace paragraph [0101] on pages 37-38 with the following amended paragraph:

[0101] The binding pocket comprises the amino acid residues that are unique (non-conserved between homologues) to a molecule; these residues allow that binding pocket to adopt a unique shape and allow for distinct binding site specificity. The binding pocket may comprise the amino acid residues found within the near vicinity (5 Å or 8 Å) of a bound inhibitor. The binding pocket may also comprise residues which are shown by the structure coordinates to be important for maintaining the structural integrity of the amino acid residues that either directly bind to inhibitor or form the binding pocket. Therefore, in one embodiment, the binding pocket of human ACE2 comprises amino acids residues N149, D269, R273, F274, H345, P346, A348, D367, T371, H374, E375, H378, E398, E402, R481, L503, F504, H505, Y510, S511, F512, Y515 and E564 according to ~~Figures 3A or 3B~~ Figure 3A or 3B. The importance of these additional residues is noted in Example 9. Residue F274 and T371 are not conserved in tACE and are positioned to line the S1' site of the ACE2-inhibitor1 structure; therefore, these residues may be responsible for binding site specificity. Residue E398 and S511 form a hydrogen bond and project into the location where a second chloride anion binding site is located in the tACE-inhibitor structure; therefore, in part distinguishing tACE-inhibitor binding from ACE2-inhibitor binding. Residue E564

is the only non-conserved residue of the residues that act as ~~mechnical~~mechanical hinges upon active site closure (other hinge residues include A396, N397, L539, H540, P565 and W566). Residue K481 in tACE is a lysine. Residue L503 and F512, as compared with K511 and Y520 (the corresponding residues in tACE), lack the ability to form hydrogen bonds with the terminal carboxylate of the inhibitor. Without being bound by theory, this may contribute to binding site specificity in ACE2. In another embodiment, the binding pocket of human ACE2 comprises amino acids residues N149, D269, R273, F274, H345, P346, A348, D367, T371, H374, E375, H378, E398, E402, R481, L503, F504, H505, Y510, S511, F512 and Y515 according to ~~Figures 3A or 3B~~ Figure 3A or 3B.

Please replace paragraph [0102] on page 39 with the following amended paragraph:

[0102] In another embodiment, the binding pocket of human ACE2 comprises amino acids residues N149, D269, R273, F274, H345, P346, A348, D367, T371, H374, E375, H378, E402, F504, H505, Y510, F512, and Y515 according to ~~Figures 3A or 3B~~ Figure 3A or 3B. In a preferred embodiment, the binding pocket of human ACE2 comprises amino acids residues N149, D269, R273, F274, P346, T371, Y510, and F512 according to ~~Figures 3A or 3B~~ Figure 3A or 3B.

Please replace paragraph [0108] on page 40 with the following amended paragraph:

[0108] The variations in coordinates discussed above may be generated because of mathematical manipulations of the ACE2 structure coordinates. For example, the structure coordinates set forth in ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B could undergo crystallographic permutations, fractionalization, integer additions or subtractions, inversion, or any combination of the above.

Please replace paragraph [0116] on page 43 with the following amended paragraph:

[0116] For the purpose of this invention, any molecule, molecular complex, binding pocket, motif, domain thereof or portion thereof that is within a root mean square deviation for backbone atoms (N, C α , C, O) when superimposed on the relevant backbone atoms described by structure coordinates listed in ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B are encompassed by this invention.

Please replace paragraph [0127] on pages 49-50 with the following amended paragraph:

[0127] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues N149, D269, R273, F274, H345, P346, A348, D367, T371, H374, E375, H378, E398, E402, R481, L503, F504, H505, Y510, S511, F512, Y515 and E564 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0128] on pages 50-51 with the following amended paragraph:

[0128] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues N149, D269, R273, F274, H345, P346, A348, D367, T371, H374, E375, H378, E398, E402, R481, L503, F504, H505, Y510, S511, F512 and Y515 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0129] on page 51 with the following amended paragraph:

[0129] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues N149, D269, R273, F274, H345, P346, A348, D367, T371, H374, E375, H378, E402, F504, H505, Y510, F512, and Y515 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino

acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0130] on pages 51-52 with the following amended paragraph:

[0130] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues N149, D269, R273, F274, P346, T371, Y510, and F512 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0131] on page 52 with the following amended paragraph:

[0131] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues R273, F274, P346, and T371 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0132] on pages 52-53 with the following amended paragraph:

[0132] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues R273, F274, H345, P346, T371, H374, E375, H378, E402, H505, Y510 and Y515 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater

than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0133] on page 53 with the following amended paragraph:

[0133] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues R273, F274, H345, P346, T371, H374, E375, H378, E402, H505, and Y515 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0134] on pages 53-54 with the following amended paragraph:

[0134] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid

residues R273, F274, H345, P346, D367, T371, H374, E375, H378, E402, H505, Y510, R514 and Y515 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0135] on page 54 with the following amended paragraph:

[0135] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues N149, D269, R273, F274, H345, P346, A348, D367, T371, H374, E375, H378, E402, F504, H505, Y510, F512, R514, and Y515 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one

embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0136] on pages 54-55 with the following amended paragraph:

[0136] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues N149, D269, R273, F274, P346, T371, E398, R481, L503, Y510, S511, F512, and E564 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0137] on page 55 with the following amended paragraph:

[0137] In one embodiment, the present invention provides a molecule or molecular complex comprising all or part of an ACE2 binding pocket defined by structure coordinates of a set of amino acid residues that correspond to human ACE2 amino acid residues N149, D269, R273, F274, H345, P346, A348, D367, T371, H374, E375, H378, E398, E402, R481, L503, F504, H505, Y510, S511, F512, R514,

Y515 and E564 according to ~~Figures 3A or 3B~~ Figure 3A or 3B, wherein the root mean square deviation of the backbone atoms between said amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3.0 Å. In one embodiment, the RMSD is not greater than about 2.0 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.8 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. In one embodiment, the RMSD is not greater than about 0.3 Å. In one embodiment, the RMSD is not greater than about 0.2 Å.

Please replace paragraph [0138] on pages 55-56 with the following amended paragraph:

[0138] Another embodiment of this invention provides a molecule or molecular complex comprising a protein defined by structure coordinates of a set of amino acid residues which correspond to human ACE2 amino acid residues according to Figure 1A, 2A, 3A or 3B, wherein the root mean square deviation between said set of amino acid residues of said molecule or molecular complex and said ACE2 amino acid residues is not more than about 3 Å. In one embodiment, the RMSD is not greater than about 2 Å. In one embodiment, the RMSD is not greater than about 1.7 Å. In one embodiment, the RMSD is not greater than about 1.5 Å. In one embodiment, the RMSD is not greater than about 1.0 Å. In one embodiment, the RMSD is not greater than about 0.5 Å. Alanines were built in the molecular model of Figures 1A and 2A due to weak electron density. For the purpose of this invention, human ACE2 amino acid residues refer to the amino acid identities of the full-length human ACE2 protein ~~shown in SEQ ID NO:4.~~

Please replace paragraph [0140] on pages 56-57 with the following amended paragraph:

[0140] According to another embodiment, this invention provided a machine-readable data storage medium, comprising a data storage material encoded with machine-readable data, wherein said data defines the above-mentioned molecules or molecular complexes. In one embodiment, the data defines the above-mentioned binding pockets by comprising the structure coordinates of said amino acid residues according to ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B. To use the structure coordinates generated for ACE2, homologues thereof, or one of its binding pockets, it is at times necessary to convert them into a three-dimensional shape. This is achieved through the use of commercially or publicly available software that is capable of generating a three-dimensional structure of molecules or portions thereof from a set of structure coordinates. The three-dimensional structure may be displayed as a graphical representation on a machine, such as a computer.

Please replace paragraph [0156] on page 62 with the following amended paragraph:

[0156] In one embodiment, the structure coordinates of said molecules or molecular complexes are produced by homology modeling of at least a portion of the structure coordinates of ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B. Homology modeling can be used to generate structural models of ACE2 homologues or other homologous proteins based on the known structure of ACE2. This can be achieved by performing one or more of the following steps: performing sequence alignment between the amino acid sequence of a molecule (possibly an unknown molecule) against the amino acid sequence of ACE2;

identifying conserved and variable regions by sequence or structure; generating structure co-ordinates for structurally conserved residues of the unknown structure from those of ACE2; generating conformations for the structurally variable residues in the unknown structure; replacing the non-conserved residues of ACE2 with residues in the unknown structure; building side chain conformations; and refining and/or evaluating the unknown structure.

Please replace paragraph [0194] on pages 81-82 with the following amended paragraph:

[0194] The structure coordinates set forth in ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B can also be used in obtaining structural information about other crystallized molecules or molecular complexes. This may be achieved by any of a number of well-known techniques, including molecular replacement.

Please replace paragraph [0195] on page 82 with the following amended paragraph:

[0195] According to one embodiment of this invention, the machine-readable data storage medium comprises a data storage material encoded with a first set of machine readable data which comprises the Fourier transform of at least a portion of the structure coordinates set forth in ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B or homology model thereof, and which, when using a machine programmed with instructions for using said data, can be combined with a second set of machine readable data comprising the X-ray diffraction pattern of a molecule or molecular complex to determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

Please replace paragraph [0196] on pages 82-83 with the following amended paragraph:

[0196] In another embodiment, the invention provides a computer for determining at least a portion of the structure coordinates corresponding to X-ray diffraction data obtained from a molecule or molecular complex, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structure coordinates of ACE2 according to ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B or homology model thereof;

(b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises X-ray diffraction data obtained from said molecule or molecular complex; and

(c) instructions for performing a Fourier transform of the machine-readable data of (a) and for processing said machine-readable data of (b) into structure coordinates.

Please replace paragraph [0197] on page 83 with the following amended paragraph:

[0197] For example, the Fourier transform of at least a portion of the structure coordinates set forth in ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B or homology model thereof may be used to determine at least a portion of the structure coordinates of ACE2 homologues. In one embodiment, the molecule is an ACE2 homologue. In another embodiment, the molecular complex is selected from the group consisting of ACE2 complex and ACE2 homologue complex.

Please replace paragraph [0198] on pages 83-84 with the following amended paragraph:

[0198] Therefore, in another embodiment this invention provides a method of utilizing molecular replacement to obtain structural information about a molecule or a molecular complex of unknown structure wherein the molecule or molecular complex is sufficiently homologous to ACE2, comprising the steps of:

- (a) crystallizing said molecule or molecular complex of unknown structure;
- (b) generating an X-ray diffraction pattern from said crystallized molecule or molecular complex;
- (c) applying at least a portion of the ACE2 structure coordinates set forth in one of ~~Figures 1A, 2A, 3A or 3B~~ Figures 1A, 2A, 3A or 3B or a homology model thereof to the X-ray diffraction pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown; and
- (d) generating a structural model of the molecule or molecular complex from the three-dimensional electron density map.

Please replace paragraph [0200] on page 84 with the following amended paragraph:

[0200] By using molecular replacement, all or part of the structure coordinates of ACE2 as provided by this invention or homology model thereof (and set forth in ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B) can be used to determine the structure of

a crystallized molecule or molecular complex whose structure is unknown more quickly and efficiently than attempting to determine such information *ab initio*.

Please replace paragraph [0202] on page 85 with the following amended paragraph:

[0202] Thus, this method involves generating a preliminary model of a molecule or molecular complex whose structure coordinates are unknown, by orienting and positioning the relevant portion of ACE2 protein according to ~~Figures 1A, 2A, 3A or 3B~~ Figure 1A, 2A, 3A or 3B within the unit cell of the crystal of the unknown molecule or molecular complex so as best to account for the observed X-ray diffraction pattern of the crystal of the molecule or molecular complex whose structure is unknown. Phases can then be calculated from this model and combined with the observed X-ray diffraction pattern amplitudes to generate an electron density map of the structure whose coordinates are unknown. This, in turn, can be subjected to any well-known model building and structure refinement techniques to provide a final, accurate structure of the unknown crystallized molecule or molecular complex (E. Lattman, "Use of the Rotation and Translation Functions", in *Meth. Enzymol.*, 115, pp. 55-77 (1985); M. G. Rossmann, ed., "The Molecular Replacement Method", *Int. Sci. Rev. Ser.*, No. 13, Gordon & Breach, New York (1972)).